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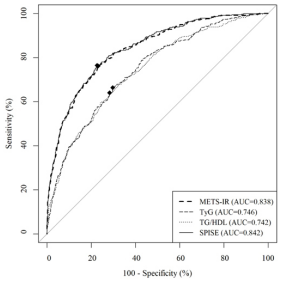
Participants

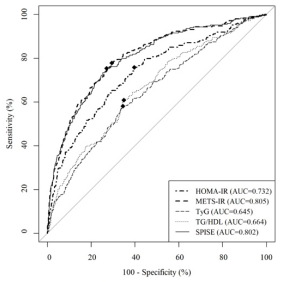
1,594 children and adolescents from the KNHANES

Result

ROC curves for insulin resistance



ROC curves for ALT elevation



Cutoff points

	Insulin resistance	ALT elevation
SPISE	< 7.75	< 8.01
METS-IR	> 31.84	> 31.61

Conclusion

SPISE and METS-IR are useful predictive markers for insulin resistance and elevated ALT levels in children and adolescents.

Highlights

- **SPISE and METS-IR are reliable predictors of insulin resistance in youth.**
- **SPISE and METS-IR predict elevated liver transaminases effectively in youth.**
- **Cutoff points for SPISE and METS-IR in IR are <7.75 and >31.84, respectively.**

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Comparison of SPISE and METS-IR and Other Markers to Predict Insulin Resistance and Elevated Liver Transaminases in Children and Adolescents

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Background: Studies on predictive markers of insulin resistance (IR) and elevated liver transaminases in children and adolescents are limited. We evaluated the predictive capabilities of the single-point insulin sensitivity estimator (SPISE) index, metabolic score for insulin resistance (METS-IR), homeostasis model assessment of insulin resistance (HOMA-IR), the triglyceride (TG)/high-density lipoprotein cholesterol (HDL-C) ratio, and the triglyceride-glucose index (TyG) for IR and alanine aminotransferase (ALT) elevation in this population.
Methods: Data from 1,593 participants aged 10 to 18 years were analyzed using a nationwide survey. Logistic regression analysis was performed with IR and ALT elevation as dependent variables. Receiver operating characteristic (ROC) curves were generated to assess predictive capability. Proportions of IR and ALT elevation were compared after dividing participants based on parameter cutoff points.
Results: All parameters were significantly associated with IR and ALT elevation, even after adjusting for age and sex, and predicted IR and ALT elevation in ROC curves (all $P<0.001$). The areas under the ROC curve of SPISE and METS-IR were higher than those of TyG and TG/HDL-C for predicting IR and were higher than those of HOMA-IR, TyG, and TG/HDL-C for predicting ALT elevation. The proportions of individuals with IR and ALT elevation were higher among those with METS-IR, TyG, and TG/HDL-C values higher than the cutoff points, whereas they were lower among those with SPISE higher than the cutoff point.
Conclusion: SPISE and METS-IR are superior to TG/HDL-C and TyG in predicting IR and ALT elevation. Thus, this study identified valuable predictive markers for young individuals.

Keywords: Adolescent; Biomarkers; Child; Insulin resistance; Non-alcoholic fatty liver disease

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a chronic condition characterized by the accumulation of excessive fat in the liver, often accompanied by elevated liver enzyme levels [1,2]. It contributes significantly to liver fibrosis, an advanced liver disease, and is closely associated with various cardiometabolic risk factors, such as obesity, dyslipidemia, and insulin resistance (IR) [1,3]. Due to the association between hepatic steatosis with IR and metabolic dysfunction, the concept of metabolic dysfunction-associated steatotic liver disease (MASLD), as a steatotic liver disease (SLD) accompanied by metabolic risk factors in patients without significant alcohol consumption, has recently been proposed [4].

Alanine aminotransferase (ALT) is considered a useful laboratory test for screening for MASLD in children [1,5]. Pediatric

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guidelines recommend further evaluation, including imaging studies, for NAFLD in children with elevated ALT levels [6]. Although predictive markers of SLD have been suggested in adults, investigations of biomarkers of MASLD and abnormal liver enzymes in children are limited [7-9].

IR induces increases in serum levels of fatty acids, insulin, and glucose. This, in turn, facilitates the accumulation of fatty acids and triglycerides (TG) in the liver, which is associated with the pathogenesis of SLD and with increased liver enzyme levels [1,10,11]. The glucose clamp technique is the gold standard for measuring IR; however, it is cumbersome for children because it requires multiple blood samples obtained through intravenous catheters [10]. Consequently, the homeostasis model assessment of insulin resistance (HOMA-IR) index has been proposed as a reliable alternative method [10,12]. Nevertheless, the insulin test lacks a standardized protocol, is not routinely performed in children, and requires fasting blood samples [13]. Moreover, HOMA-IR levels and the proportion of individuals with prediabetes has increased among Korean adolescents in recent years [14,15]. Therefore, studies investigating simple non-insulin-based biomarkers for predicting IR in children are necessary.

Recently, the single-point insulin sensitivity estimator (SPISE) index, derived from high-density lipoprotein cholesterol (HDL-C), TG, and the body mass index (BMI), has been proposed as a surrogate predictor of IR. This index was developed using data from a large European cohort that underwent oral glucose tolerance tests and euglycemic-hyperinsulinemic clamp tests [16]. The predictive capability of the SPISE index was shown to be comparable to that of HOMA-IR and superior to that of the TG/HDL-C ratio for identifying IR [17,18]. Although various markers, including the TG/HDL-C ratio and triglyceride-glucose index (TyG), and the metabolic score for insulin resistance (METS-IR), have been suggested to be useful predictors for IR and SLD in adults, few pediatric studies have compared these markers for the prediction of IR, MASLD, and abnormal liver enzymes [7-9,19].

In this study, we investigated the validity of predictive markers, including the SPISE index, METS-IR, TG/HDL-C, and TyG, for IR and elevated liver transaminase levels, in children and adolescents. We analyzed data from the Korea National Health and Nutrition Examination Survey (KNHANES). Our objectives were specifically to (1) compare the predictive capability of SPISE and other parameters for IR and ALT elevation, and (2) establish optimal cutoff values for SPISE and other parameters to predict IR and ALT elevation in this population.

METHODS

Study design and participants

This retrospective study analyzed data from 1,593 individuals aged 10 to 18 years who participated in the KNHANES between 2019 and 2021. The study design and workflow are shown in Supplementary Fig. 1. KNHANES, a nationally representative survey conducted in Korea, uses a complex, stratified, and multistage probability sampling method to select participants from the entire population. The survey was administered by the Korea Centers for Disease Control and Prevention and included health and nutrition surveys and medical examinations. These datasets provide comprehensive insights into individuals' health statuses, behaviors, socioeconomic statuses, and laboratory test results. To ensure accuracy, sampling weights were applied to account for differences in selection probabilities and nonresponse rates. The weighted data were adjusted to represent the demographics of the Korean population accurately by sex and age groups [20].

This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Yongin Severance Hospital (IRB No: 9-2024-0074). All participants volunteered and provided written consent prior to participation.

Study variables

Participants' weights were measured using a Giant 150N scale (HANA, Seoul, Korea), with an accuracy of 0.1 kg. Heights were assessed using a stadiometer (range, 850 to 2,060 mm) (Seriter, Holtain Ltd., Crymych, UK), with an accuracy of 0.1 cm. BMI was calculated as weight in kilograms divided by height in meters squared. Height, weight, and BMI were converted to standard deviation scores (SDS) based on the 2017 Korean National Growth Charts [21]. Children were categorized into three groups based on their BMI: those with a BMI <85th percentile were considered to have normal weight, those with a BMI ranging from the 85th to 95th percentile were classified as being overweight, and those with a BMI ≥95th percentile were considered to have obesity [21,22].

Laboratory analysis

Blood samples were collected from the antecubital vein after an overnight fast of at least 8 hours. The samples were pro-

cessed immediately and then refrigerated. Serum levels of aspartate aminotransferase (AST) and ALT were measured using commercially available kits (Pureauto S ALT, Daiichi Pure Chemicals, Tokyo, Japan), employing ultraviolet light measurement instead of the pyridoxal-5-phosphate method. Serum insulin levels were determined using the Wizard 1470 gamma counter (PerkinElmer, Turku, Finland). Plasma levels of fasting glucose, total cholesterol, HDL-C, and TG were measured using the Hitachi Automatic Analyzer 7600/7600-210 (Hitachi, Tokyo, Japan).

HOMA-IR was calculated by multiplying fasting insulin (mg/dL) by fasting glucose (mg/dL) and then dividing the result by 22.5. IR was defined as an HOMA-IR value above the 95th percentile for each age and sex group, according to Korean reference data [23]. ALT elevation was defined as ALT levels higher than 26 and 22 IU/L in males and females, respectively, in the absence of hepatitis B viral infection [3,24].

Definition of the markers

The parameters were calculated using the following formulae:

HOMA-IR = [glucose (mg/dL) × insulin (IU/L)]/405 [23]

TyG = Ln [fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2] [10]

SPISE = $[600 \times \text{HDL-C (mg/dL)}^{0.185}]/[\text{TG (mg/dL)}^{0.2} \times \text{BMI (kg/m}^2)^{1.338}]$ [16]

METS-IR = ln [(2 × glucose, mg/dL)+TG (mg/dL)] × BMI (kg/m^2)/[ln (HDL-C, mg/dL)] [17].

Statistical analysis

Categorical variables are presented as numbers (weighted percentages), and continuous variables as weighted means (standard errors). Student's *t*-test was performed to compare mean values of continuous variables, and the Rao-Scott chi-square test was used to compare categorical variables. Logistic regression analyses were conducted with IR and ALT elevation as dependent variables, to examine the association between the markers and conditions. The optimal cutoff points for the markers were determined using Youden's index. Receiver operating characteristic (ROC) curves were generated to evaluate and compare the diagnostic values of these parameters for predicting IR and ALT elevation. Pairwise comparisons of parameters' area under the receiver operating characteristic curve (AUC) were performed using Delong's method. The proportion of participants with IR and ALT elevation was analyzed using the Rao-Scott chi-square test after dividing subjects according to the cutoff points of each parameter. All statistical analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA) and R version 4.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P<0.05$.

RESULTS

Baseline characteristics with respect to IR and ALT elevation

Table 1 shows baseline characteristics with respect to IR and ALT elevation. Age, HDL-C, and SPISE were lower in the IR group than in the non-IR group. Conversely, weight SDS, BMI SDS, glucose, insulin, total cholesterol, TG, AST, ALT, HOMA-IR, METS-IR, TyG, and TG/HDL-C, as well as the proportion of males, obesity, and ALT elevation, were higher in the IR group than in the non-IR group. Participants with elevated ALT had higher age, weight SDS, BMI SDS, glucose, insulin, total cholesterol, TG, AST, ALT, HOMA-IR, METS-IR, TyG, and TG/HDL-C, and a higher proportion of males, obesity, and IR than did those with normal ALT. HDL-C and SPISE values were lower in participants with elevated ALT than in those with normal ALT.

Logistic regression analyses

In logistic regression analyses, glucose, TG, METS-IR, TyG, and TG/HDL-C exhibited positive associations with IR, whereas HDL-C and SPISE showed negative correlations with IR (all $P<0.001$) (Table 2). These associations remained significant even after adjusting for age and sex (all $P<0.001$). With regard to ALT elevation, glucose, TG, METS-IR, TyG, and TG/HDL-C displayed positive associations with IR, whereas HDL-C and SPISE exhibited negative associations ($P=0.016$ for glucose and $P<0.001$ for all other variables). These associations also remained significant after adjusting for age and sex ($P=0.018$ for glucose and $P<0.001$ for other variables).

Cutoff points and AUC of the parameters for predicting IR and ALT elevation

Table 3, Fig. 1 show a summary of the results from the ROC curve analyses and corresponding AUCs, along with their respective 95% confidence intervals (CIs), for the parameters predicting IR and ALT elevation. The cutoff points for IR prediction were as follows: >31.84 for METS-IR, >9.01 for TyG, >1.71 for TG/HDL-C, and <7.75 for SPISE. The AUCs for these

Table 1. Baseline characteristics of the participants with respect to IR and ALT elevation

Characteristic	Total (n=1,593)	Non-IR (n=1,215)	IR (n=378)	P value	Normal ALT (n=1,345)	ALT elevation (n=248)	P value
Age, yr	14.19±0.08	14.31±0.08	13.79±0.18	0.007	14.10±0.08	14.68±0.19	0.006
Male sex, %	53.46±1.37	50.24±1.56	64.07±2.80	<0.001	49.66±1.46	74.55±3.04	<0.001
Height SDS	0.37±0.04	0.30±0.04	0.58±0.06	<0.001	0.34±0.04	0.49±0.10	0.181
Weight SDS	0.36±0.05	–0.01±0.04	1.56±0.08	<0.001	0.15±0.04	1.53±0.10	<0.001
BMI SDS	0.23±0.05	–0.19±0.04	1.61±0.10	<0.001	–0.02±0.05	1.61±0.12	<0.001
BMI percentile, %				<0.001			<0.001
Normal	73.66±1.51	85.86±1.10	33.42±3.14		80.66±1.38	34.78±3.61	
Overweight	9.56±0.81	7.15±0.82	17.50±2.15		8.64±0.79	14.69±2.51	
Obesity	16.78±1.28	6.99±0.84	49.07±3.28		10.70±1.15	50.53±3.81	
Glucose, mg/dL	92.10±0.23	90.84±0.24	96.26±0.46	<0.001	91.87±0.25	93.38±0.58	0.017
Insulin, mIU/L	15.52±0.40	10.83±0.14	31.00±1.20	<0.001	13.78±0.32	25.19±1.61	<0.001
Total cholesterol, mg/dL	163.46±0.88	161.49±0.93	169.95±1.75	<0.001	162.20±0.91	170.46±2.55	0.002
HDL-C, mg/dL	51.70±0.32	53.19±0.34	46.82±0.60	<0.001	52.51±0.34	47.21±0.65	<0.001
TG, mg/dL	87.87±1.66	78.03±1.47	120.33±3.82	<0.001	83.87±1.65	110.09±4.50	<0.001
AST, IU/L	21.53±0.31	20.64±0.31	24.49±0.73	<0.001	19.27±0.17	34.08±1.40	<0.001
ALT, IU/L	18.09±0.53	14.77±0.38	29.04±1.58	<0.001	12.58±0.15	48.69±2.10	<0.001
HOMA-IR	3.60±0.10	2.45±0.03	7.41±0.30	<0.001	3.18±0.08	5.93±0.40	<0.001
METS-IR	30.97±0.27	28.67±0.19	38.58±0.62	<0.001	29.57±0.25	38.78±0.64	<0.001
TyG	8.87±0.02	8.76±0.02	9.23±0.03	<0.001	8.83±0.02	9.11±0.04	<0.001
TG/HDL-C	1.84±0.04	1.56±0.04	2.76±0.11	<0.001	1.72±0.04	2.50±0.12	<0.001
SPISE	9.18±0.10	9.94±0.09	6.69±0.13	<0.001	9.62±0.09	6.72±0.15	<0.001
ALT elevation, %	15.26±1.08	9.56±1.02	34.04±2.71	<0.001	-	-	-
IR, %	23.26±1.38	-	-	-	18.11±1.35	51.90±3.62	<0.001

Values are presented as mean±standard error.
IR, insulin resistance; ALT, alanine aminotransferase; SDS, standard deviation score; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; AST, aspartate aminotransferase; HOMA-IR, homeostasis model assessment of insulin resistance; METS-IR, the metabolic score for insulin resistance; TyG, triglyceride-glucose index; SPISE, single-point insulin sensitivity estimator.

parameters were 0.838 (95% CI, 0.816 to 0.861) for METS-IR, 0.746 (95% CI, 0.719 to 0.774) for TyG, 0.742 (95% CI, 0.714 to 0.770) for TG/HDL-C, and 0.842 (95% CI, 0.820 to 0.865) for SPISE (all P<0.001). The AUCs of METS-IR and SPISE were significantly higher than those for TyG and TG/HDL-C (Fig. 1, Supplementary Table 1).

To predict ALT elevation, the following cutoff values were established: >3.04 for HOMA-IR, >31.61 for METS-IR, >9.01 for TyG, >1.74 for TG/HDL-C, and <8.005 for SPISE. The corresponding AUCs were 0.732 (95% CI, 0.696 to 0.768), 0.805 (95% CI, 0.774 to 0.835), 0.645 (95% CI, 0.607 to 0.683), 0.663 (95% CI, 0.626 to 0.701), and 0.801 (95% CI, 0.770 to 0.832) for HOMA-IR, METS-IR, TyG, TG/HDL-C, and SPISE, respectively (all P<0.001). The AUCs for HOMA-IR, METS-IR, and SPISE were significantly higher than those for TyG and TG/HDL-C (Fig. 1, Supplementary Table 1). Additionally, the AUCs for METS-IR and SPISE were significantly higher than those for HOMA-IR.

Proportion of the participants with IR and ALT elevation relative to the cutoff points of each parameter

Fig. 2 shows the proportions of individuals with IR and ALT elevation based on the cutoff points for each parameter. The proportion of individuals with IR was significantly greater among those with METS-IR, TyG, and TG/HDL-C values above the cutoff points, whereas it was significantly lower in

Table 2. Odds ratio of IR and ALT elevation according to each parameter

Variable	IR		ALT elevation	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Unadjusted				
Glucose	1.139 (1.111–1.169)	<0.001	1.032 (1.006–1.059)	0.016
TG	1.017 (1.014–1.020)	<0.001	1.009 (1.006–1.012)	<0.001
HDL-C	0.927 (0.912–0.943)	<0.001	0.941 (0.923–0.960)	<0.001
HOMA-IR			1.260 (1.160–1.369)	<0.001
METS-IR	1.229 (1.197–1.261)	<0.001	1.161 (1.121–1.202)	<0.001
TyG	7.789 (5.638–10.762)	<0.001	2.901 (2.092–4.024)	<0.001
TG/HDL-C	2.082 (1.811–2.393)	<0.001	1.444 (1.283–1.625)	<0.001
SPISE	0.508 (0.464–0.557)	<0.001	0.584 (0.531–0.643)	<0.001
Adjusting for age and sex				
Glucose	1.135 (1.105–1.166)	<0.001	1.034 (1.006–1.062)	0.018
TG	1.017 (1.014–1.020)	<0.001	1.009 (1.006–1.012)	<0.001
HDL-C	0.927 (0.912–0.943)	<0.001	0.950 (0.932–0.970)	<0.001
HOMA-IR			1.304 (1.195–1.422)	<0.001
METS-IR	1.255 (1.219–1.292)	<0.001	1.152 (1.112–1.194)	<0.001
TyG	7.691 (5.596–10.571)	<0.001	3.038 (2.187–4.220)	<0.001
TG/HDL-C	2.071 (1.808–2.373)	<0.001	1.437 (1.279–1.614)	<0.001
SPISE	0.486 (0.439–0.537)	<0.001	0.601 (0.545–0.662)	<0.001

Logistic regression analyses were performed with IR and ALT elevation as dependent variables.
IR, insulin resistance; ALT, alanine aminotransferase; OR, odds ratio; CI, confidence interval; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; METS-IR, the metabolic score for insulin resistance; TyG, triglyceride-glucose index; SPISE, single-point insulin sensitivity estimator.

participants with SPISE values below the cutoff point (all $P<0.001$). The proportion of individuals with elevated ALT was significantly greater in participants with HOMA-IR, METS-IR, TyG, and TG/HDL-C values above the cutoff points, but significantly lower in those with SPISE values above the cutoff point (all $P<0.001$).

DISCUSSION

Our findings contribute to the existing literature by providing specific cutoff values and demonstrating the predictive capability of TG/HDL-C, TyG, METS-IR, and SPISE for IR. Additionally, we found that these parameters, along with HOMA-IR, significantly predicted IR and ALT elevation, even after adjusting for age and sex, in children and adolescents. Furthermore, METS-IR and SPISE were superior to the TG/HDL-C and TyG in predicting both IR and ALT elevation. The prevalence of IR was 4–5 times higher in participants with high TG/HDL-C, TyG, and METS-IR, or low SPISE, than in those with low TG/HDL-C, TyG, and METS-IR, or high SPISE. Similarly, the prevalence of ALT elevation was 2–3 times higher in participants with high TG/HDL-C, TyG, and METS-IR, or low SPISE, than in those with low TG/HDL-C, TyG, and METS-IR, or high SPISE.

In this study, all parameters were derived from TG, which were significantly related to IR, even after adjusting for age and sex. Since it was first suggested as a novel parameter for IR prediction in 2008, the potential of the TyG for IR prediction has been validated in various studies [10,25,26]. In a systematic review, the cutoff values and AUCs of the TyG for IR varied from 4.43 to 4.78 and from 0.59 to 0.88, respectively, among adults [26]. In a previous study, the cutoff point and AUC of the TyG for IR were 8.26 and 0.72, respectively, among youths [10]. In a meta-analysis, the hazard ratio of TG/HDL-C for cardiovascular events was 1.08 [27]. The association of IR with TG can be explained as follows. First, insulin suppresses lipolysis, whereas

Table 3. Cutoff values and AUC for each parameter for predicting IR and ALT elevation

Variable	Cutoff	AUC (95% CI)	*P* value	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
IR								
METS-IR	>31.839	0.838 (0.816–0.861)	<0.001	0.771 (0.770–0.772)	0.758 (0.758–0.759)	0.761 (0.761–0.762)	0.492 (0.491–0.493)	0.916 (0.916–0.917)
TyG	>9.008	0.746 (0.719–0.774)	<0.001	0.687 (0.686–0.687)	0.718 (0.717–0.718)	0.710 (0.710–0.711)	0.424 (0.423–0.425)	0.883 (0.883–0.883)
TG/HDL-C	>1.707	0.742 (0.714–0.770)	<0.001	0.703 (0.702–0.703)	0.684 (0.683–0.685)	0.688 (0.688–0.689)	0.403 (0.402–0.403)	0.884 (0.883–0.884)
SPISE	<7.749	0.842 (0.820–0.865)	<0.001	0.723 (0.722–0.724)	0.814 (0.813–0.814)	0.793 (0.792–0.793)	0.541 (0.540–0.541)	0.906 (0.906–0.907)
ALT elevation								
HOMA-IR	>3.040	0.732 (0.696–0.768)	<0.001	0.750 (0.749–0.751)	0.619 (0.619–0.620)	0.639 (0.639–0.640)	0.262 (0.261–0.262)	0.932 (0.932–0.933)
METS-IR	>31.610	0.805 (0.774–0.835)	<0.001	0.800 (0.799–0.801)	0.701 (0.700–0.701)	0.716 (0.715–0.716)	0.325 (0.324–0.326)	0.951 (0.951–0.951)
TyG	>9.010	0.645 (0.607–0.683)	<0.001	0.588 (0.586–0.589)	0.665 (0.665–0.666)	0.653 (0.653–0.654)	0.240 (0.239–0.241)	0.900 (0.899–0.900)
TG/HDL-C	>1.740	0.663 (0.626–0.701)	<0.001	0.631 (0.630–0.632)	0.652 (0.652–0.653)	0.649 (0.649–0.650)	0.246 (0.246–0.247)	0.908 (0.907–0.908)
SPISE	<8.005	0.801 (0.770–0.832)	<0.001	0.778 (0.777–0.780)	0.724 (0.724–0.725)	0.732 (0.732–0.733)	0.337 (0.336–0.338)	0.948 (0.948–0.948)

AUC, area under the receiver operating characteristic curve; IR, insulin resistance; ALT, alanine aminotransferase; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; METS-IR, the metabolic score for insulin resistance; TyG, triglyceride-glucose index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SPISE, single-point insulin sensitivity estimator; HOMA-IR, homeostasis model assessment of insulin resistance.

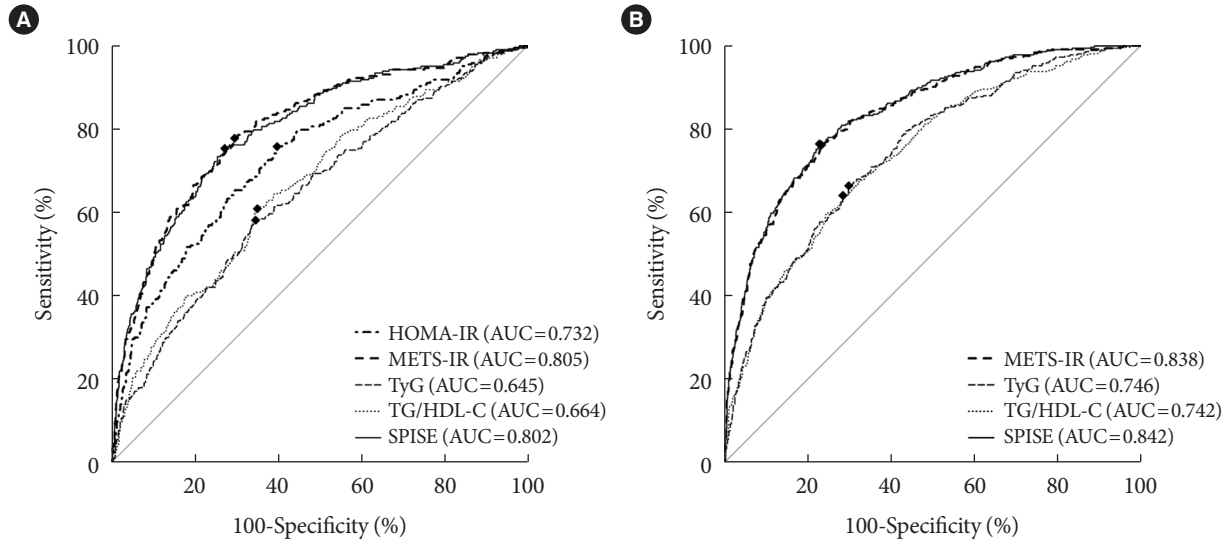

Fig. 1. Receiver operating characteristic curve of each parameter for predicting (A) insulin resistance and (B) alanine transaminase elevation. The dots on the curves represent cutoff points of each parameter. HOMA-IR, homeostasis model assessment of insulin resistance; AUC, area under the receiver operating characteristic curve; METS-IR, metabolic score for insulin resistance; TyG, triglyceride-glucose index; TG/HDL-C, triglyceride/high-density lipoprotein cholesterol; SPISE, single-point insulin sensitivity estimator.

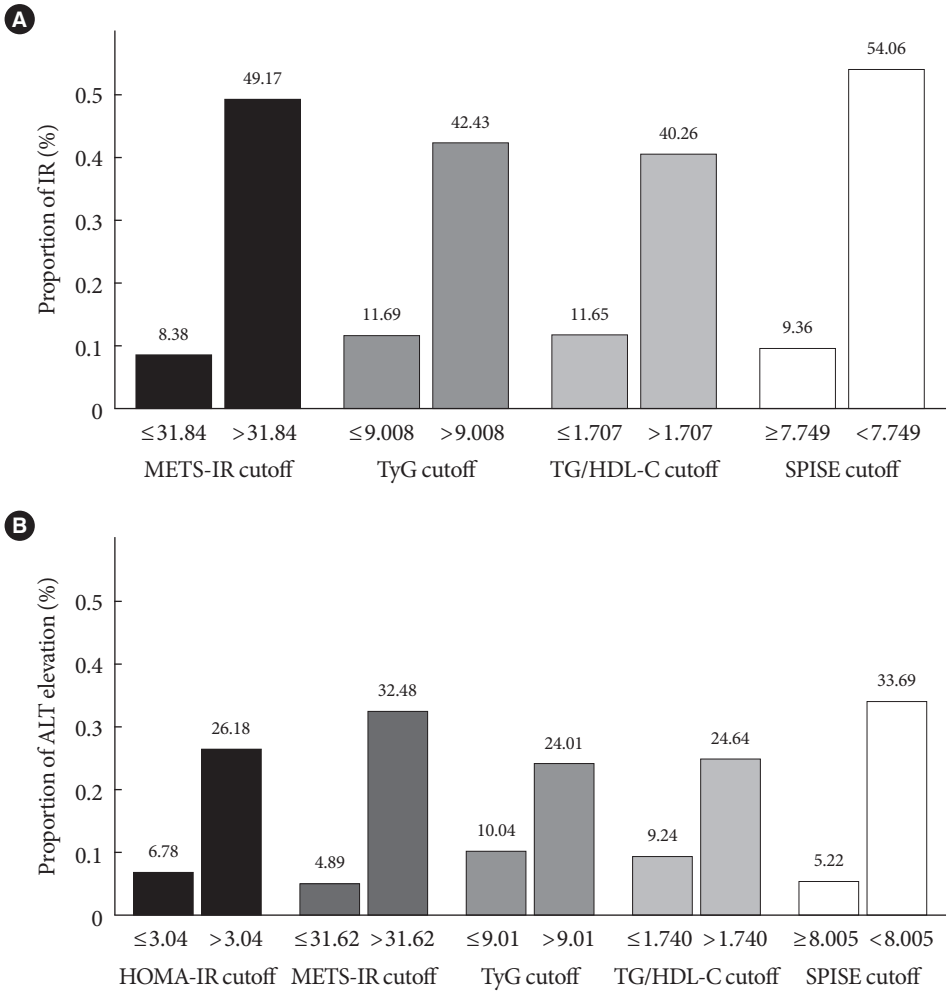

Fig. 2. Proportion of participants with (A) insulin resistance (IR) and (B) alanine transaminase (ALT) elevation relative to the cutoff points of each parameter.The numbers on the bars indicate the proportion (%) of participants. METS-IR, metabolic score for insulin resistance; TyG, triglyceride-glucose index; TG/HDL-C, triglyceride/high-density lipoprotein cholesterol; SPISE, single-point insulin sensitivity estimator; HOMA-IR, homeostasis model assessment of insulin resistance.

lipolysis is suppressed in individuals with IR [10,25]. Thus, an increase in serum TG levels can be induced by the flux of free fatty acids from adipose tissue into the bloodstream. Second, impaired muscle glucose metabolism due to hypertriglyceridemia can induce IR [28]. Moreover, an increase in inflammatory cytokine levels decreases HDL-C levels in individuals with visceral obesity, which is usually associated with IR [29,30]. This association may contribute to the IR-predictive ability of parameters derived from HDL-C.

In this study, the proportion of IR was three times higher in participants with than in those without ALT elevation, and the proportion of ALT elevation was 3.5 times higher in participants with than in those without IR. In a meta-analysis, the proportion of NAFLD was twice as high in individuals with type 2 diabetes mellitus as in those without this condition [31]. In a population-based study, the odds ratio (OR) of ALT elevation among youths with prediabetes was 1.85 [14]. IR plays a key role in the pathogenesis of MASLD by promoting hepatic lipid accumulation due to overproduction of very-low-density lipoprotein. Moreover, anti-lipolytic effect of insulin is decreased under IR condition, which promotes production of free fatty acids. In addition, *de novo* lipogenesis is promoted by hyperinsulinemia [1,9,32]. Obesity and hypertriglyceridemia exacerbate this process by contributing to adipose tissue dysfunction, chronic inflammation, and dysregulation of lipid metabolism [1,11,33]. Moreover, the association between

HDL-C and both obesity and IR may contribute to the relationship between HDL-C and NAFLD [9,29,30].

Based on the aforementioned evidence, various markers related to IR have been suggested as predictive markers of NAFLD and MASLD. In a meta-analysis conducted among adults, the AUC of the TyG for MASLD was 0.75 [34]. In a Spanish study in adults, the cutoff point and AUC of the TG/HDL-C for MASLD were 3.7 and 0.747, respectively [9]. In a Korean study conducted in adults, the ORs of the TyG and HOMA-IR for NAFLD were 2.94 and 1.93, respectively [7]. Additionally, in a previous study, the cutoff point and AUC of the TyG for NAFLD were 8.47 and 0.76, respectively, in children and adolescents [33].

In our study, SPISE and METS-IR were superior to other parameters for predicting IR and ALT elevation. TyG and TG/HDL-C are simple parameters based on association of TG, glucose, and HDL-C with IR and cardiovascular risk, but their formulae were not developed through statistical analysis [25,35]. HOMA-IR has been widely used, but it is dependent on insulin measurement, which is not a routine laboratory test and has limited standardization [10,36]. To overcome limitations of the existing markers, SPISE, a formula derived from TG and HDL-C as well as BMI, was developed using mathematical algorithm for IR prediction in a cohort study [16]. The study assessed IR using euglycemic-hyperinsulinemic clamp test, a gold standard for IR, in cohort of 1,260 adults and 29 adolescents. METS-IR was developed using linear regression analysis with anthropometric measurements and biochemical tests as independent variables, which was validated using euglycemic-hyperinsulinemic clamp test [17]. In a cross-sectional study, SPISE exhibited superiority over HOMA-IR and the TG/HDL-C for IR prediction among adults, yielding an AUC of 0.88 [37]. Similarly, in another cross-sectional study, SPISE was suggested to be a valuable predictor of IR, achieving an AUC of 0.795 in children [38]. In a longitudinal study, SPISE was superior to HOMA-IR and the quantitative insulin sensitivity check index for prediction of dysglycemia among children with overweight and obesity [39]. A cohort study reported that METS-IR was superior to HOMA-IR and TyG in predicting major adverse cardiac events in adults [18]. Moreover, in a separate cohort study, the AUC for the time-dependent ROC curve of METS-IR was superior to that of HOMA-IR in predicting incident NAFLD in adults [40]. In another study, AUCs of SPISE, METS-IR, and HOMA-IR for prediction of metabolic dysfunction-associated fatty liver disease were 0.730, 0.730, and 0.724 in males, and 0.721, 0.728, and 0.702 in females, respectively [41]. The inclusion of BMI in the formulae for SPISE and METS-IR may contribute to their superiority, given the close relationship between IR, hepatic steatosis, and obesity [3,10,23,42,43]. Notably, adolescents with obesity exhibited higher HOMA-IR values than did those without obesity, with a mean difference of 2.22, as reported in a meta-analysis [42]. Furthermore, previous studies have demonstrated that combining the TyG with BMI enhances its predictive capability for IR and NAFLD [10,11]. Finally, while the HOMA-IR and the TyG are well-established and straightforward tools, they are limited in capturing the multifaceted nature of metabolic disturbances associated with IR. Conversely, the SPISE and the METS-IR provide more comprehensive insights into metabolic health.

This study had several limitations. First, it was a retrospective study limited to Korean youth. Therefore, generalizing the findings to other ethnicities or age groups might prove challenging. Second, we assessed ALT elevation instead of MASLD, because information on imaging studies or biopsies was not provided in the KNHANES. Third, the body composition, including muscle and fat mass, was not considered when assessing obesity. Fourth, confounding factors related to IR, such as birth weight, physical activity, and nutrition were not considered in this study [44]. Fifth, IR was defined using HOMA-IR, even though the euglycemic-hyperinsulinemic clamp test is the gold standard for IR definition. Despite these limitations, strength of this study is that it compared various markers of IR in a large sample of children and adolescents and provided cutoff values of these markers for this population.

In conclusion, our study demonstrated the potential of TG/HDL-C, TyG, METS-IR, SPISE, and HOMA-IR for predicting IR and ALT elevation. Additionally, the recently developed parameters, SPISE and METS-IR, were shown to be superior to the TG/HDL-C and TyG for these predictions. We also demonstrated that the cutoff values of these parameters were useful for assessing the risk of IR and ALT elevation in children and adolescents. These results suggest that the SPISE and METS-IR can serve as effective markers for screening IR and abnormal liver enzymes in this population.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2024.0302.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: K.S., Y.J.K.
Acquisition, analysis, or interpretation of data: all authors.
Drafting the work or revising: K.S., Y.J.K.
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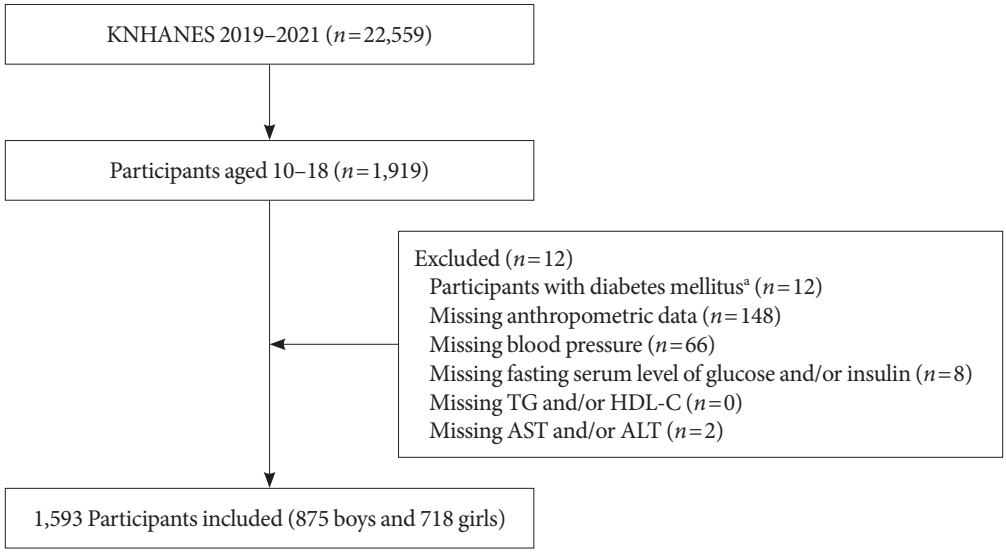
Supplementary Table 1. Comparison of AUC among each parameter for predicting IR and ALT elevation

Variable	HOMA-IR	METS-IR	TyG	TG/HDL-C	SPISE
IR					
METS-IR		Ref			
TyG		<0.001	Ref		
TG/HDL-C		<0.001	0.409	Ref	
SPISE		0.208	<0.001	<0.001	Ref
ALT elevation					
HOMA-IR	Ref				
METS-IR	<0.001	Ref			
TyG	<0.001	<0.001	Ref		
TG/HDL-C	0.001	<0.001	0.006	Ref	
SPISE	<0.001	0.262	<0.001	<0.001	Ref

Values are presented as *P* values. Delong's method was used to perform pairwise comparisons between areas under the receiver operating curves for the parameters.

AUC, area under the receiver operating characteristic curve; IR, insulin resistance; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment of insulin resistance; METS-IR, the metabolic score for insulin resistance; TyG, triglyceride-glucose index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SPISE, single-point insulin sensitivity estimator.



Supplementary Fig. 1. Flowchart of the study population. KNHANES, Korea National Health and Nutrition Examination Survey; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase. [a]Participants with fasting serum glucose level ≥126 mg/dL and/or glycosylated hemoglobin ≥6.5%.